EDITORIAL

Echocardiography for Embolic Risk Stratification in Atrial Fibrillation: Improvement of CHA_2DS_2-VASc in the Era of New Oral Anticoagulants

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It is well known that atrial fibrillation (AF) is the most frequent sustained cardiac rhythm disturbance, occurring in between 1 and 2% of the general population. AF confers a fivefold risk of stroke and one in five of all strokes plus an unknown number of "cryptogenic strokes" is attributable to AF. (1) The mean incidence of a disabling stroke in AF patients is 2.5%/year, which increase to 7% if TIA and silent stroke are included.

Therefore, in the management of antithrombotic therapy in patients with AF the balance between embolic and hemorrhagic risk is essential. In these patients the first task for the physician is the risk stratification for embolism and hemorrhage with all the available score systems. This is the basis for the "individualized antithrombotic therapy", which sometimes remain an ideal goal, to best treat AF against the two great risks: cerebral embolism and major hemorrhages.

THE CHA_2DS_2-VASC AND OTHER MODELS FOR EMBOLIC AND HEMORRHAGIC RISK STRATIFICATION

For a long time, the most widely accepted and used stroke risk scheme has been the $CHADS_2$ score, derived from the Stroke Prevention in Atrial Fibrillation investigators and the Atrial Fibrillation Investigators criteria, also suggested by the European (1) and American (2) guidelines on AF. The advantages of $CHADS_2$ were due to the simplicity of the scheme (only five clinical features were calculated: congestive heart failure, hypertension, age >75 years, diabetes, and prior stroke or transient ischemic attack) and to an acceptable predictive value for stroke. The major disadvantage of this stroke risk scheme was the large differences in embolic risk in AF patients with low ($CHADS_2$=0) or moderate embolic scores ($CHADS_2$=1). Consequently, in the choice of anticoagulation with warfarin or aspirin for these patients, physicians have been mostly driven by the hemorrhagic risk and by individual characteristics. (3)

More recently, the addition of supplementary embolic risk factors (namely age > 65 years, vascular disease and female gender) with the new acronym "CHA_2DS_2-VASc", improved the predictive value of the schematic score, being endorsed as the preferred method for embolic risk stratification by the European Society of Cardiology in its recent edition of AF guidelines. (4) This new score is more useful to select truly low risk patients (those with CHA_2DS_2-VASc score of 0) that can be left without any anticoagulant therapy (neither aspirin) and to raise the profile of moderate-high risk patients that now show a CHA_2DS_2-VASc score of >=2 where the anticoagulation is strongly suggested.

The difficult choice is still present for patients with high hemorrhagic risk or relative contraindication to anticoagulation especially when the embolic risk is not so high (e.g. CHA_2DS_2-VASc score of 1). In these cases the score risk scheme mostly used for predicting hemorrhages is the HASBLED, which share some of the clinical predictors with the CHA_2DS_2-VASc embolic risk score system (Figure 1). The wise clinician has to identify those few predictors typical only of embolic risk or of hemorrhagic risk. As specified later, echocardiographic predictors have the precious particularity of increasing mostly the embolic risk.

The importance of the embolic/hemorrhagic balance of risk has been recently boosted in a study that changes the rule of "anticoagulate all patients with a $CHADS_2$ score of 1". Among these patients, those showing also a CHA_2DS_2-VASc score of 1 (26% of the total number) showed a low embolic risk (0.9% / year), who are unlikely to benefit from oral anticoagulant therapy because of the hemorrhagic risk, while anticoagulation is mandatory when the CHA_2DS_2-VASc

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Rev Argent Cardiol 2013;81:102-106. http://dx.doi.org/10.7775/rac.v81.i2.2522
SEE RELATED ARTICLE: http://dx.doi.org/10.7775/rac.v81.i2.1904. Rev Argent Cardiol 2013;81:133-138.

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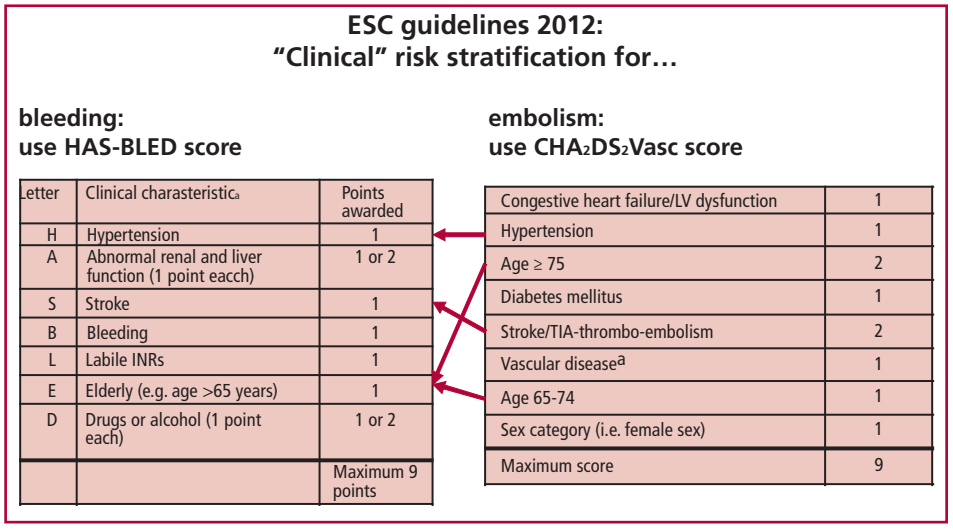

Fig. 1. 2012 ESC Guidelines for bleeding and thromboembolic clinical risk stratification.

score is 2 or more, because of the high embolic risk (2.1% / year). (5)

THE WORLD IS CHANGING: THE ADVENT OF NEW ORAL ANTICOAGULANTS

Nowadays it is very difficult to test the efficacy of any new stratification scheme for the embolic risk in order to decide not to anticoagulate AF patients, due to the fact that most AF patients are already anticoagulated. Moreover, all the previous analysis have to be reconsidered in the light of the complete change of anticoagulation with the advent of new oral anticoagulants. It is well known the higher efficacy and safety of direct thrombin inhibitors (dabigatran) and anti Xa (rivaroxaban and apixaban).

The use of these new anticoagulants lowers the threshold of embolic risk for the beginning of anticoagulation and raise the point of a cost effectiveness analysis. First of all the new oral anticoagulants were demonstrated effective and safe at all levels of embolic risk, starting from a value of $CHADS_2=1$. Despite this general effectiveness at all $CHADS_2$ and CHA_2DS_2-VASc values, a different level of efficacy of each new anticoagulant has been observed for ischemic stroke, hemorrhagic stroke, major hemorrhages and net clinical benefit. Moreover the dosages of some new anticoagulants can be titrated on the basis of ischemic and hemorrhagic risk, therefore the wise clinician will use schematic clinical scores and echocardiography to suggest the right new anticoagulant and the right dosage individualized for each patient.

ECHOCARDIOGRAPHY IN EMBOLIC RISK STRATIFICATION

With so many new anticoagulants and in the complex situation of a large number of AF patients with moderate embolic and hemorrhagic risk, the classical stratification schemes give us only a partial embolic /hemorrhagic balance. It is clear that all physicians cannot use a single new anticoagulant blindly in all patients, so echocardiography can switch a light on, as demonstrated by Allende et al. (6).

In fact, it is a routine to perform a complete echocardiography in all patients undergoing therapy for AF, especially those with new onset AF or undergoing electrical or pharmacologic cardioversion. Despite the echocardiographic information is not adequately emphasized in epidemiologic studies, it is recognized essential in the choice of any therapy or management strategy. (1) In the difficult decision of the lifelong anticoagulation for these patients, it is important to consider the pathophysiology of thromboembolism secondary to AF.

LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION

Usually the first goal of echocardiography in AF patients is the characterization of AF etiology and the analysis of systolic and diastolic function. In fact, almost all the clinical risk factors included in the CHA_2DS_2-VASc score scheme (hypertension, diabetes, old age, congestive heart failure, vascular pathology) influence systolic and diastolic function directly or indirectly.

Despite the original $CHADS_2$ score did not include left ventricular (LV) systolic function as a predictive variable (the investigators did not have access to echocardiographic results), the 2006 guidelines nevertheless allowed LV dysfunction as a risk factor for stroke. (2) Successively, thanks to echocardiographic results, (7) the 2010 ESC guidelines1 included in the $CHADS_2$ scheme the moderate or severe LV systolic dysfunction, defined as an ejection fraction $<=40\%$, as a surrogate for heart failure.

Despite the mechanisms linking clinical risk factors to ischemic stroke are incompletely defined in patients with AF, their contribution is largely mediated by auricular dysfunction and thrombi, and only seldom by aortic plaques, LV thrombi or other possible sources.

In addition to LV systolic and diastolic function,

the altered intra-atrial thrombogenic milieu (indicated by parameters of left atrial thrombogenicity at transesophageal echocardiography, such as LA thrombus and/or spontaneous echocardiographic contrast) is a marker for an increased cardiovascular death independent of clinically associated risk factors, such as hypertension, diabetes mellitus, smoking, congestive heart failure, and prior myocardial infarction. (8) The presence of left atrial (LA) appendage dysfunction (evidenced as dense echocontrast or low emptying LA appendage velocities) is associated with symptomatic, but also with silent cerebral embolisms at follow up. (9)

The linkage between clinical risk factors and left appendage thrombi is perhaps mediated by the ventricular systolic and diastolic dysfunction with effects on LA dynamics and pressure. So the left appendage dysfunction is very often the ultimate pathophysiologic link between clinical risk factors and thromboembolic event (Figure 2). (10, 11)

Confirming this pathophysiologic cascade from LV dysfunction to LA thrombosis, the present paper of Allende and coll. demonstrates the progressive increase in the risk of LA thrombus associated to the CHA_2DS_2-VASc score (3.6 ± 1.6 with thrombus vs. 2.7 ± 1.6 without thrombus, P: 0.024). The Authors also describe previous studies showing a direct correlation between clinical embolic risk factors (represented by the CHADS2 score and/or LV dysfunction) and LA thrombi or other echocardiography risk factors for embolism. (12, 13)

The novel part of the present study is the addition of different degrees of LV dysfunction (categorized according different LV ejection fraction thresholds of 35%, 45% and 55%) to improve the CHA_2DS_2-VASc model in predicting the presence of LA thrombi.

Among limitations, it is important to consider that the high percentage of LA thrombi observed by Allende and coll is typical of this group of AF patients mostly studied before cardioversion (107 cardioversions in the total number of 129 patients), mostly without a chronic anticoagulant therapy (a INR>2 at the moment of the study was only present in 29% of the patients).

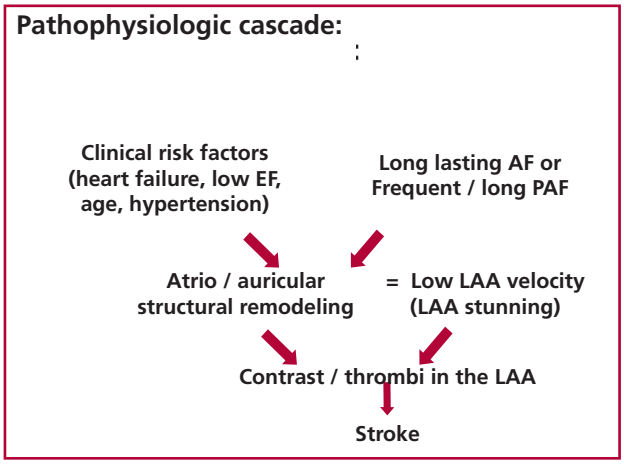

Fig. 2. Pathophysiological cascade

Moreover, with this new proposed model that added LV systolic function as variable to the CHA_2DS_2-VASc score, the mean score increased in both groups (with and without LA thrombi), with only a modest increase in the area under the ROC curve with superimposed confidence intervals between the two models. Only few patients (a total number of 4) showed a high score (corresponding to 8 or 9) with this modified CHA_2DS_2-VASc-LVF model. A clear independence of the predictive power of LV dysfunction from the clinical heart failure was not demonstrated with multivariate analysis.

LEFT ATRIAL AND APPENDAGE DYSFUNCTION AND THROMBOSIS

Another valuable analysis from Allende and coll. demonstrated that a CHA_2DS_2-VASc score <2 did not ensure thrombus absence in the AF studied population. In fact, differently from previous studies, (13-16) they found thrombi in LA appendage in 2 patients with CHA_2DS_2-VASc score = 1 and in 1 patient with score = 0. This observation raises the interesting debate about the negative predictive power of a low $CHADS_2$ (=0) or CHA_2DS_2-VASc (0 or 1) score in detecting the absence of thrombi.

The essential part of this debate is the absolute necessity of the analysis of LA and LA appendage function in patients with AF. In fact also Allende et al. describe that "Although emptying velocity of the LA appendage and density of spontaneous contrast were not the primary objective of the study, their relationship with presence of thrombus was retrospectively analyzed." Interestingly, they found that the presence and density of spontaneous contrast (P=0.005) and a low LA appendage velocity (<0.4 m/s) (P=0.015) showed a clear association with thrombi. No patient with absence of both indicators of slower atrial blood flow presented intracavitary masses.

In fact, using transthoracic and transesophageal echocardiography, the contractile function of left appendage, both in sinus rhythm and in AF, can be evaluated directly (calculating the 2D fractional area change, the M mode fractional shortening (17) or the PW Doppler left appendage emptying velocity) or indirectly (looking for left appendage thrombi or spontaneous echocontrast). All the data coming from the specific multivariate analysis of echocardiographic risk factors for thromboembolic events in the SPAF III (7, 18) and other trials, (9) showed that the only features independently associated with increased thromboembolic risk are left appendage thrombi (relative risk [RR] 2.5, $p < 0.04$), dense spontaneous echocontrast (RR 3.7, $p < 0.001$), left appendage peak emptying velocities ≤20 cm/s (RR 1.7, p<0.008) and complex aortic plaques (RR 2.1, p<0.001). (Table 1) Further information on LA appendage morphology and function is

Valvular risk factors	
Mitral stenosis	
Mechanical prosthetic heart valvea	
Clinical Risk factors (enlarged CHA_2DS_2-VASc)	**Echocardiographic risk factors**
Previous stroke, TIA or embolism	Left ventricular systolic dysfunction (EF<40%)
Age > 75 y (2 points) or 65-74 y (1 point)	
Hypertension	Left atrial dilatation
Congestive heart failure	*Complex aortic plaques
	*Left appendage thrombi or SEC (Spontaneous echo contrast)
Diabetes mellitus	Left appendage dysfunction (emptying velocities <20 cm/s and/or reduced contraction at M-mode)
Vascular disease	
Sex gender (female)	
Renal insufficiency	

* Indentifier only at TEE EF Ejection Fraction TIA Transient Ischemic Attack

Table 1. Complete risk factors analysis in patients with atrial fibrillation

also obtained with transesophageal three-dimensional echocardiography. (19)

THE IMPROVEMENT OF CHA_2DS_2-VASC IN THE ERA OF NEW ORAL ANTICOAGULANTS

In the era of new oral anticoagulants, with a higher efficacy in thromboembolism protection and a better safety for major hemorrhages, the evaluation of CHA_2DS_2-VASc and other risk score schemes is even more important, but sometimes needs refinement.

The data on novel oral anticoagulants have been evaluated in subgroup analysis for different CHA_2DS_2-VASc levels and for different age and clinical parameters. All these points affect the efficacy and safety balance, which is fundamental for the patient, but also for cost/effectiveness analysis and pharmaeconomics in this time of cost savings.

Therefore, the addition of echocardiography is fundamental in particular groups of AF patients where the choice for the introduction of warfarin or new oral anticoagulants is debatable because of a low embolic risk (CHA_2DS_2-VASc =1) and/or a high hemorrhagic risk (HASBLED>=3).

In these patients the evaluation of etiology of the AF and of the LV function is the first echocardiographic step, indicative of a indirect sign of increased embolic risk. However, the real information in AF patients comes as a second step from the LA and LA appendage: when transthoracic or transesophageal direct signs of LA appendage dysfunction are present the patient is at very high embolic risk.

This presence of thrombi or these other direct signs of embolic risk (dense spontaneous echocontrast, pulsed-wave Doppler low emptying velocity or M-Mode dysfunction of LA appendage) indicate the usage of new oral anticoagulants at their maximum dosages in all patients. Conversely, the absence of echocardiography embolic risk factors can allow a cautious behaviour, especially in patients with a high hemorrhagic risk, indicating less importance in full anticoagulation or the opportunity to use new oral anticoagulants at low dosages.

A better knowledge of AF and thrombus pathophysiology permits a more judicious use of anticoagulation: we cannot miss this great utility of echocardiography

Conflicts of interest
None declared

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